PATENT
Attorney Docket No. **CONLINCO-03681**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Asgeir Sæbo *et al.*
Serial No.: 09/271,024 Group No.: 1617
Filed: 03/17/99 Examiner: Wang
Entitled: **CONJUGATED LINOLEIC ACID COMPOSITIONS**

Declaration of Asgeir Sæbo

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Dated: 12/13/2002 By: Susan M. McClintock
Susan M. McClintock

I, Asgeir Sæbo, state as follows:

1. My present position is Director of Research, Natural AS.

2. I have reviewed the above captioned patent application, of which I am an inventor, the Office Action mailed August 13, 2002, and the Cook, Nilsen and Pariza references cited as prior art.

3. I have conducted repeats of the conjugation methods described in WO97/18320 to Cain.

4. In the repeat of Cain, the conjugation conditions were the same as those described in Example 6 of WO97/18320. The results of the conjugation reactions were analyzed by GC-MS. The results are attached at Tab 1. As can be seen, this conjugation method resulted in a conjugated linoleic acid composition comprising approximately 3.49% c11,t13 CLA and 2.24% t9,t11and t10,t12 CLA. The t8,c10 isomer co-elutes with the c9,t11 isomers, but almost always occurs in a one to one proportion to the c11,t13 isomer. I note that this method is very similar to the method utilized in the Sugano reference, which was discussed in my previous Declaration.

My work confirms that these methods produce CLA with relatively high levels of undesirable isomers.

5. The Examiner states at page 3 of the Office Action that Cain teaches CLA compositions that are composed of 48.9% c9,t11 and 51.1% t10,c12 CLA, and that the analysis was carried out with gas chromatography and no other isomer of conjugated linoleic acid is detected. However, this does not mean that the other isomers were not present, as was found in my repeat of Cain. This discrepancy is explainable by the facts that 1) methods for the analysis of CLA compositions in 1996 were rather crude and 2) Cain may have simply chosen not to include non-active isomers when reporting their results. Improved methods for detecting the various isomers of CLA were not developed until well after the 1995 priority date of Cain. This fact is substantiated by Yurawecz *et al.* (attached at Tab 2), who state "the CLA products analyzed in this study were found to contain up to 12 geometric and positional CLA isomers. These findings are based on appropriate and improved analytical methodologies [including gas chromatography techniques] that have only recently been developed." (Yurawecz, *p.* 281). Thus, Cain et al. may not have conducted an analysis which could detect the isomers in questions. Consideration of Example 18 of Cain et al. supports this analysis. The inventors state that their compositions, produced by the method of Example 6, contained 63.8% CLA, of which 48.9% was the cis 9, trans 10 isomer and 51.1% was the trans 10, cis 12 isomer. This means that the inventors provide no analysis of the remaining 36.2% of their composition. The 8,10; 11,13; and trans-trans isomers that are discriminated against in the present invention and detected in my repeat of Cain could well have been present in this fraction.

6. With respect to the Nilsen reference, I note that it does not provide any method of producing conjugated linoleic acid having less than 1% 8,10; 11,13; and trans-trans isomers.

7. With respect to the Pariza application, I note that the passages cited by the Examiner (column 4, line 50, bridging column 8, line 68) do not teach preparation of CLA in amounts suitable for incorporation into acylglycerides. Instead, the HPLC purified isomers are produced only for use as chromatography standards. Furthermore, Pariza does not disclose using the purified isomers for any other use but as standards. In other words, Pariza does not disclose using the purified isomers to prepare acylglycerides or food products, or using a combination of (i.e., c9,t11 and t10,c12) purified isomers in any product.

8. I further understand that the Examiner has requested evidence of the criticality, or

unexpected benefit of CLA compositions containing less than 1% of 8,10; 11,13, and trans-trans octadecadienoic acid isomers. I refer the Examiner to the publication attached at Tab 2, Yurawecz et al., Variation in isomer distribution in commercially available conjugated linoleic acid, Fett/Lipid 101:277-282 (1999). This study, by researchers at the U.S. Food and Drug Administration (U.S.F.D.A.), was "undertaken to determine the content and distribution of CLA isomers in commercially available CLA capsules and liquid products with labels stating to contain CLA." In brief, the authors of the Yurawecz *et al.* publication note that:

> While it has not been established, which isomer(s) is (are) responsible for the reported beneficial properties of CLA, it is generally thought that anticarcinogenicty is due to rumenic acid [c9,t11 octadecadienoic acid]. The nutritional and physiological effects, if any, of other CLA isomer(s) in commercially available CLA preparations are not known.

(Yurawecz, *p.* 280). In an additional reference cited within Yurawecz *et al.*, (published by members of the Yurawecz group) it was found that the 11 *cis*, 13 *trans*-18:2 isomer was found to was found to accumulate preferentially in heart phospholipids and specifically in heart and liver diphosphatidylglycerol (DPG) of pigs feed commercial CLA mixtures. Yurawecz *et al.* note that in response to their "findings that 11 *cis*, 13 *trans*-18:2 was selectively incorporated into DPG . . . , a major supplier of commercial CLA preparations recently modified [their production] process to eliminate the 11 *cis*, 13 *trans*-18:2 isomer." (Yurawecz, *p.* 281). Thus, it is desirable to control the amounts of CLA isomers of unknown function in CLA compositions.

9. This conclusion is also supported by Adlof et al., Changes in Conjugated Linoleic Acid Composition Within Samples Obtained from a Single Source, Lipids 36(3):315-17 (2001), attached hereto at Tab 3. At page 315, the authors state:

> If indeed certain daily levels of CLA intake are required to produce suggested health benefits in humans, changes in concentrations of specific CLA isomers could significantly impact these effects. Care must be taken to analyze the CLA used in human and animal studies.

10. I further declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Asgeir Sæbo

Date: Dec. 10. 2002